Increased Burden of Cerebral Small Vessel Disease in Patients With Type 2 Diabetes and Retinopathy

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OBJECTIVE

We sought to examine the presence and severity of brain small vessel disease (SVD) in patients with type 2 diabetes and diabetic retinopathy (DR) compared with those without DR.

RESEARCH DESIGN AND METHODS

We evaluated 312 patients with type 2 diabetes without previous cardiovascular disease (men 51%; mean age 57 years; age range 40–75 years); 153 patients (49%) had DR. MRI was performed to evaluate the presence and severity (age-related white matter changes scale) of white matter lesions (WMLs) and lacunes, and transcranial Doppler ultrasound was used to measure the Gosling pulsatility index (PI) of the middle cerebral artery (MCA).

RESULTS

The prevalence of lesions of cerebral SVD (WML and/or lacunes) was higher in patients with DR (40.2% vs. 30.1% without DR, $P = 0.04$). Age ($P < 0.01$) and systolic blood pressure ($P = 0.02$) were associated with the presence of SVD. The severity of SVD was associated with age and the presence of DR ($P < 0.01$ and $P = 0.01$, respectively). Patients with DR showed a higher MCA PI compared with those without DR ($P < 0.01$). Age, systolic and diastolic blood pressure, and retinopathy and its severity were associated with an increased MCA PI ($P < 0.01$ for all variables). A positive correlation was found between MCA PI values and the presence and severity of SVD ($P < 0.01$ for both variables).

CONCLUSIONS

Patients with type 2 diabetes who have DR have an increased burden of cerebral SVD compared with those without DR. Our findings suggest that the brain is a target organ for microangiopathy, similar to other classic target organs, like the retina.

PATHOPHYSIOLOGY/COMPLICATIONS

Patients with type 2 diabetes mellitus have an increased risk of cardiovascular (CV) morbidity and mortality. The chronic deleterious effects of hyperglycemia are classically separated into microvascular and macrovascular complications. In addition to the classic target organs of microangiopathy, such as the retina or the kidneys, the brain has also been described more recently as a target organ for diabetic microvascular complications (1).

Cerebral small vessel disease (SVD) is the term commonly used to describe a syndrome of clinical, cognitive, neuroimaging, and neuropathological findings that

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are thought to arise from the disease affecting the perforating cerebral arterioles, capillaries, and venules, resulting in brain damage in the cerebral white and deep gray matter (2). At MRI examination, SVD, as outlined in the Standards for Reporting Vascular Changes on Neuroimaging (STRIVE) position paper (3), can show distinct forms, most typically symptomatic small subcortical infarcts, subclinical lacunes, white matter hyperintensities, and cerebral microbleeds. Leukoaraiosis or white matter disease is a descriptive term to denominate the cerebral white matter lesions (WMLs) frequently seen on brain imaging, which are considered to be a radiological sign of tissue damage produced by chronic ischemia caused by SVD. Leukoaraiosis and its severity are associated with cognitive decline (4) and a higher risk of stroke (5). Studies of the relationship between diabetes and WMLs disease have shown conflicting results. Several studies (6,7) have reported an association between diabetes and WMLs, whereas others have not confirmed this association. A very recent study (8) demonstrated more advanced white matter injury in patients with type 2 diabetes with chronic kidney disease. Lacunar infarcts or lacunes are small noncortical infarcts caused by the occlusion of small penetrating branches of large cerebral arteries. Several studies (9) have shown that diabetes is an independent risk factor for lacunar strokes. Finally, in patients with diabetes, the presence and severity of retinopathy are associated with future CV events, including ischemic stroke (10,11).

Another method used for the evaluation of cerebral SVD is the measurement of vascular resistance using a pulsatility index (PI) by transcranial Doppler ultrasonography (TCD), which has long been proposed to reflect the vascular resistance of the small vessels. The PI has been shown to be increased in association with the presence of WMLs (12), and also in elderly subjects (13). In patients with diabetes, Lee et al. (14) described an increased PI of the middle cerebral artery (MCA) in a small group of 33 patients with microvascular complications (neuropathy, retinopathy, and neuropathy).

The microvascular bed of the retina mirrors the small cerebral vessels with respect to their embryological origin, anatomical features, and physiological properties (15). Cross-sectional studies performed in the general population show that people with retinal microvascular abnormalities are more likely to have concomitant cerebral infarct, WMLs, and microbleeds seen on MRI than those without retinopathy. In the Atherosclerosis Risk in Communities (ARIC) study (16), which was performed in middle-aged subjects without a history of CV disease, retinopathy was associated with cerebral infarcts. On the other hand, in the Cardiovascular Health Study (17), which was performed in elderly subjects (with a significant proportion of subjects having previous CV disease), cerebral infarcts were associated with retinal microvascular disease (arteriovenous ratio and nicking), but not with retinopathy. Moreover, prospective studies (18) that were also performed in the general population show evidence that the presence of microvascular retinal abnormalities is associated with incident stroke and subclinical infarcts. More recently, the presence of any retinopathy has also been associated with a greater progression of leukoaraiosis (19).

To our knowledge, there are no previous studies that have investigated the presence of SVD and its relationship with diabetic retinopathy (DR), and its severity in patients with type 2 diabetes without previous CV disease or established kidney disease. Thus, in the current study we sought to examine whether there was any difference in the presence and severity of several markers of cerebral SVD (WMLs, lacunes, and PI index) in a group of patients with type 2 diabetes and DR compared with those without DR, with neither patient group presenting with previous CV events.

RESEARCH DESIGN AND METHODS

Subjects

The study design and assessment of the cohort participants have been described previously by our group in a previous study (20) in which the presence and extension of carotid plaques were analyzed in patients with type 2 diabetes with and without DR. The inclusion criteria for both groups were as follows: age range 40–75 years; absence of established impaired renal function (calculated glomerular filtration rate $<$60 mL/min); and absence of known CV disease. By the study design, microalbuminuria (urine albumin/creatinine ratio $>$30 mg/g) and macroalbuminuria (urine albumin/creatinine ratio $>$299 mg/g) were also exclusion criteria in patients without DR and with DR, respectively. The clinical examination and review of patients' clinical records ruled out heart failure, any previously known CV events or associated revascularization procedures (coronary heart disease, cerebrovascular disease, and peripheral vascular disease, including previous diabetic foot disease). The general clinical, laboratory, and carotid ultrasound procedures have been described in detail elsewhere (20). Briefly, 312 patients with type 2 diabetes without previous CV events and with normal renal function were recruited from the outpatient clinic at our center. The subjects were selected based on the presence (n = 153) or absence (n = 159) of DR. However, brain MRI was performed in 289 patients (n = 146 with and n = 143 without DR) because of a contraindication for MRI study in 15 patients (claustrophobia in 13 patients) and a lack of compliance with the appointed visit in 8 patients.

The local ethics committee approved the protocol, and all patients signed the written informed consent form.

Methods

DR Classification

An experienced ophthalmologist assessed and classified retinopathy according to an international consensus on clinical DR (21), as follows: *1*) mild nonproliferative DR, microaneurysms only; *2*) moderate nonproliferative DR, more than just microaneurysms but less than severe nonproliferative DR; *3*) severe nonproliferative DR due to $>$20 intraretinal hemorrhages in each of four quadrants, definite venous beading in two or more quadrants, prominent intraretinal microvascular abnormalities in one or more quadrants, or no signs of proliferative retinopathy; and *4*) proliferative DR, indicated by neovascularization and/or vitreous/preretinal hemorrhage.

MRI Study Protocol

Brain magnetic resonance images were acquired on an Intera 1.5 T machine (Philips, Eindhoven, the Netherlands) with a standardized protocol. The protocol comprised an axial T2-weighted turbo spin-echo (repetition time [TR] 4,800 ms, echo time [TE] 120 ms, excitations 3),

T1-weighted spin-echo (TR 540 ms, TE 15 ms, excitations 2), turbo fluid-attenuated inversion recovery (TR 8,000 ms, inversion time 2,200 ms, TE 120 ms, excitations 2), and echo planar diffusion images (TR 3,900 ms, TE 95 ms, excitations 3). Lacunar infarcts were defined as focal areas ($<$20 mm in diameter) of decreased signal intensity on T1-weighted images and increased signal intensity on T2-weighted images (see example in Fig. 1). WMLs were scored according to the age-related white matter changes (ARWMC) scale (22), which is a simple and well-validated scale applicable to both computed tomography and MRI with a good interrater reliability. The degree of white matter changes is rated on a 4-point scale from 0 to 3 in five different regions (frontal, parieto-occipital, temporal, basal ganglia, and infratentorial) on the right and left sides of the brain separately, on T2 and FLAIR images. The rating scores were 0 for no lesions (including symmetrical, well-defined caps or bands), 1 for focal lesions, 2 for beginning lesion confluence of lesions, and 3 for the diffuse involvement of the entire region, with or without the involvement of U fibers. A patient was considered to have lesions of SVD if there were any WMLs and/or lacunes. To evaluate the association between SVD severity and retinopathy, patients were first categorized into two groups, taking into account the results of the assessment of WMLs obtained with the ARWMC score (group A, absence of WMLs or presence of mild WMLs [score 0–1], and group B, moderate and severe WMLs [score 2–3]). Then, for the purpose of analyzing the overall SVD severity, we classified patients in two arbitrary categories of severity of SVD. Patients included in the group with low SVD score were those with an ARWMC score of WMLs of 0 or 1 without any lacunes, and patients with just one lacune without any WMLs. Patients were classified in the SVD score with higher severity if any of the following occurred: *1*) the patient had any ARWMC score and two or more lacunes; *2*) an ARWMC score of 1 and any lacunes; or *3*) an ARWMC score of 2–3 with or without lacunes.

WMLs and lacunes were identified by a single trained neuroradiologist (J.D.) who was blinded to the patients' clinical data.

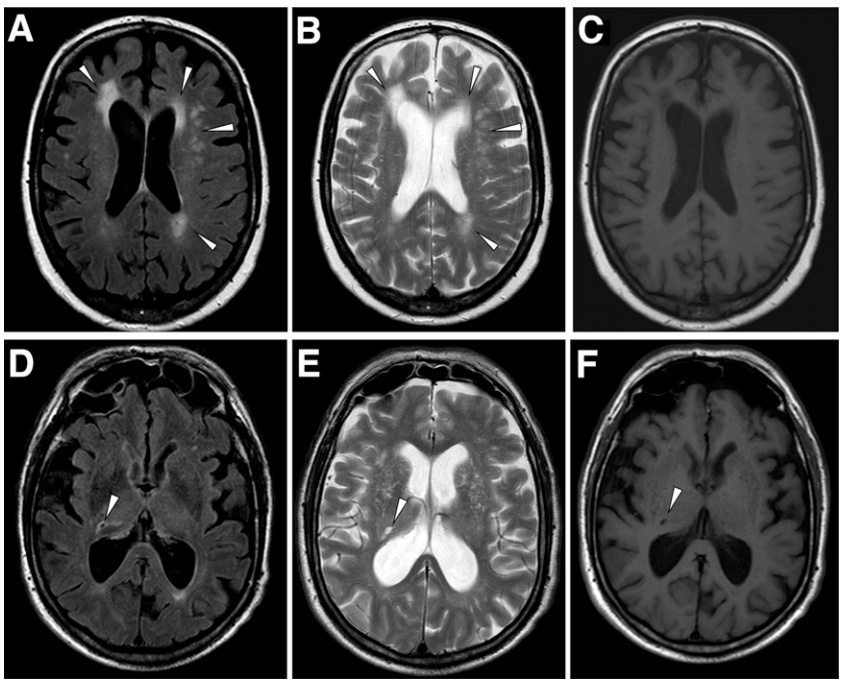

Figure 1—Magnetic resonance images illustrating WMLs and lacunar infarcts in two different patients. Arrowheads show examples of WMLs and lacunar infarct. Fluid-attenuated inversion recovery (FLAIR) (*A*), T2-weighted (*B*), and T1-weighted (*C*) images of the same patient: WMLs in the frontal and parieto-occipital areas are seen on FLAIR and T2-weighted images. FLAIR (*D*), T2-weighted (*E*), and T1-weighted (*F*) images of another patient: a right thalamic lacunar infarct is seen hypointense on T1-weighted image (*F*), hyperintense on T2-weighted, and hypointense with marginal hyperintensity on the FLAIR image.

TCD

All TCD studies were performed with a hand-held 2- to 3-MHz transcranial probe (Aplio MX; Toshiba Medical Systems, Kyoto, Japan) at the temporal bone window on both sides. The MCA mainstem was first evaluated with color Doppler, and then it was insonated at the depth giving the optimal waveform to assure a good-quality Doppler spectrum. The gosling PI of each MCA was calculated automatically as (systolic velocity-diastolic velocity)/mean velocity. The MCA was chosen because this is the cerebral artery where the best possible quality of patency of the transtemporal acoustic bone window is obtained. We only considered measurements if the Doppler spectrum waveform envelope was of very good quality and if at least four consecutive good-quality waveforms were reliable for each measurement, to ensure accurate PI values. Indeed, the mean (average of left and right) MCA PI with this quality requirement was obtained in 218 patients (115 patients with retinopathy and 103 patients without retinopathy).

Sample Size Calculation

We calculated the sample size of each group based on the hypothesis that we would find frequencies of WMLs of 25% in the group of patients with retinopathy and 10% in the group without retinopathy, with an expected dropout rate of 10%. This calculation yielded a sample size of 144 subjects in each study group, which would allow a 90% power to detect differences between groups with a significance level of $<$0.05.

Statistical Analysis

Data are given as the median and the 25th and 75th percentiles, the mean $\pm$ SD, and *n* (%). Non-normally distributed variables were log transformed to reduce skewness. The χ^2 test (or Fisher test when appropriate), Wilcoxon or Kruskal-Wallis, and *t* test or one-way ANOVA were used to assess the DR group differences in categorical, continuous non-normally, and continuous normally distributed, laboratory, clinical, MRI (WMLs and lacunes), and TCD (PI) variables. We used the Spearman correlation analysis to evaluate relationships between continuous variables and the PI. Multiple linear regression (for PI) and logistic binary regression (SVD) models were used to evaluate independent

associations between variables of interest and dependent variables (WMLs, lacunes, and PI). A significance level of $P < 0.05$ was defined. SAS version 9.2 software (SAS Institute Inc., Cary, NC) was used for all analyses.

RESULTS

Characteristics of the Study Groups

The characteristics of the study groups are shown in Table 1. To summarize, the sex distribution did not differ between groups. However, as expected by study design, age, CV risk factors, disease duration, and microalbuminuria were different between groups due to the selection criteria, the metabolic condition, or the disease stage of the participants. Patients with diabetes who have retinopathy, compared with those without retinopathy, had higher a prevalence of hypertension, higher systolic blood pressure, larger waist circumference, higher HbA_{1c} concentration, and greater urinary albumin excretion, and were more frequently treated with insulin and aspirin (Table 1). The number of patients treated with diet and/or oral antidiabetic agents only, a combination of oral agents and insulin, and insulin alone were as follows: 139, 15, and 5, respectively, in the group without DR; and 69, 66, and 18, respectively, in the group with DR ($P < 0.01$).

Cerebral SVD: WMLs and Lacunes

Figure 1 shows representative images of WMLs and lacunar infarcts. The prevalence of WMLs and lacunes was not significantly different between patients with DR (40.7% and 7%, respectively) and those without DR (30.1% and 2.7%, respectively) (Fig. 2). However, the prevalence of SVD (the presence of WMLs and/or lacunes) was higher in subjects with DR than in those without DR (42% vs. 30.1%, $P = 0.04$) (Fig. 2). WMLs were identified in 30.1%, 30.4%, and 47.1%, respectively, of patients without DR, with mild DR, and with more than mild DR ($P = 0.02$) (Table 2). The analysis of the frequency of lacunes according to retinopathy status did not reveal any differences ($P = 0.24$) (Table 2). Overall, the presence of SVD was observed in 30.1% of patients without DR, 32.1% of patients with mild DR, and in 48.3% of patients with more than mild DR ($P = 0.02$) (Table 2).

Table 1—Characteristics of the study groups

	Diabetes without DR (n = 159)	Diabetes with DR (n = 153)	P value
Sex (male/female)	82/77	76/77	0.74
Age (years)	59 (48–66)	61 (54–68)	0.01
Disease duration (years)	6 (2–10)	11 (6–20)	<0.01
Insulin treatment (n)	20 (12.6%)	84 (54.9%)	<0.01
Smoking (yes/past/never)	71/54/32	78/44/30	0.51
Antiplatelet agents (yes/no)	112/47 (29.6%)	82/71 (46.4%)	<0.01
Dyslipidemia (yes/no)	88/71 (44.7%)	79/74 (48.4%)	0.51
Hypertension (yes/no)	83/76 (47.8%)	48/105 (68.3%)	<0.01
Systolic BP (mmHg)	134 (123–145)	143 (133–159)	<0.01
Diastolic BP (mmHg)	76 (70–83)	77.5 (68.5–85.5)	0.75
HR (bpm)	75 (68–82)	77 (70–86)	0.08
BMI (kg/m^2)	30.3 (27.4–34.0)	31.1 (28.3–35)	0.25
Waist circumference (cm)	103 (96–111)	107.5 (163–114)	<0.01
Hemoglobin A_{1c} (mmol/mol)	53 (48–63)	65 (55–76)	<0.01
Hemoglobin A_{1c} (%)	7.1 (6.5–7.9)	8.1 (7.2–9.1)	<0.01
Total cholesterol (mmol/L)	184 (163–207)	181 (162–204.5)	0.99
HDL cholesterol (mmol/L)	47 (40–57)	50.5 (42–60.5)	0.03
LDL cholesterol (mmol/L)	108 (90.2–130.2)	105.4 (86.5–127.8)	0.27
Triglycerides (mmol/L)	118 (89–171)	116 (83–168)	0.62
Serum creatinine (μmol/L)	0.79 (0.69–0.92)	0.79 (0.68–0.93)	0.80
Urinary albumin/creatinine ratio (mg/g)	5.8 (3.2–11)	12.4 (6–32.7)	<0.01
Carotid plaques, n (%)	83 (52.2%)	104 (68%)	<0.01

Data are presented as the median (Q1–Q3) unless otherwise indicated. BP, blood pressure; HR, heart rate.

When the severity of SVD was assessed by the above-described score, most of the patients had a low SVD score (n = 250), and 39 patients a high SVD score. Specifically, the majority of patients with lacunes fell in the group with a high SVD score; only two patients with DR had just one lacune and were classified in the group with a low score as they did not have any other cerebral lesions. A high SVD score was observed in 8.2% of patients without DR and in 18.9% of those with DR ($P < 0.01$) (Fig. 2). A higher SVD score was observed according to increasing severity of the retinopathy status ($P < 0.01$) (Table 2).

In the next step, we investigated whether the following variables were also associated with SVD: age, sex, measures of adiposity, tobacco use, antiplatelet treatment, antidiabetic treatment, HbA_{1c} level, dyslipidemia, total and LDL cholesterol levels, carotid plaques, systolic and diastolic blood pressure, hypertension, heart rate, creatinine level, and microalbuminuria. Age (median 57 vs. 64 years, $P < 0.01$), systolic blood pressure (137 vs. 143 mmHg, $P < 0.01$), a previous diagnosis of hypertension (52.4% vs. 67.3%, $P = 0.01$), the presence of carotid plaques (52.4% vs. 67.3%, $P = 0.01$), and the presence of microalbuminuria as a dichotomous variable (11.4% vs. 20.2%, $P = 0.04$) were associated with the absence/presence of SVD. However, when variables associated with SVD, including the presence or degree of retinopathy, were considered together in a multiple stepwise regression analysis, only age (β-estimate 0.0651, $P < 0.01$) and systolic blood pressure (β-estimate 0.0173, $P = 0.02$) were independently associated with the presence of SVD.

We also analyzed the above-mentioned variable for association with a higher severity of SVD (high SVD score). Age (median 59 vs. 63 years, $P < 0.01$), systolic blood pressure (138 vs. 146 mmHg, $P < 0.01$), a previous diagnosis of hypertension (55.6% vs. 71.8%, $P = 0.06$), the presence of carotid plaques (55.2% vs. 74.4%, $P = 0.02$), microalbuminuria (continuous variable, median 7.8 vs. 13.0 mg/g, $P = 0.02$), and the presence of microalbuminuria (dichotomous variable, 12.4% vs. 28.2%, $P < 0.01$) were associated with the absence/presence of a high SVD score. However, when variables associated with a high SVD score, including degree

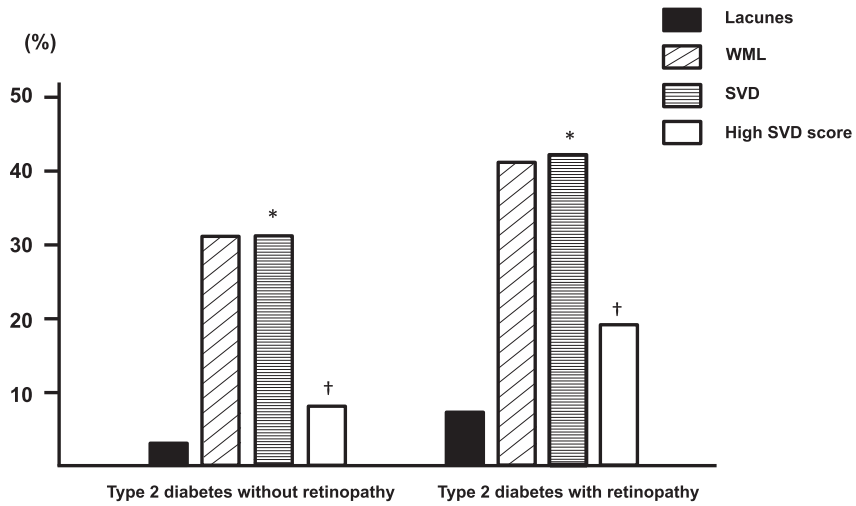

Figure 2—Frequency and severity of cerebral SVD (WMLs and lacunes) in the two study groups: patients with type 2 diabetes with and without DR. High SVD score: $*P = 0.04$; $\dagger P < 0.01$. Frequency ($*P = 0.04$) and severity ($\dagger P < 0.01$) of SVD were higher in patients with DR compared with those without DR.

of retinopathy, were considered together in a multiple stepwise regression analysis, only age (β-estimate 0.0482, $P = 0.02$) and systolic blood pressure (β-estimate 0.0238, $P = 0.01$) were independently associated with a high SVD score. When, instead of the degree of retinopathy, we included the presence/absence of retinopathy, age (odds ratio [OR] 1.06 [95% CI 1.01–1.10], $P < 0.01$), and the presence of retinopathy (OR 2.65 [95% CI 1.25–5.63], $P = 0.01$) in the model, the variables were associated with high SVD score.

PI

The median MCA PI was higher in patients with retinopathy ($n = 103$, median 1.06 [Q1–Q3 0.93–1.20]) compared with those without DR ($n = 115$, median 0.92 [Q1–Q3 0.80–1.02]) ($P < 0.01$). The median MCA PI increased gradually with the presence and degree of DR. The median MCA PI was 0.92 (Q1–Q3 0.80–1.02), 0.94 (Q1–Q3 0.85–1.11), and 1.11 (Q1–Q3 1.01–1.26), respectively, in patients without DR ($n = 115$), with mild DR ($n = 46$), and with more than mild DR ($n = 57$) ($P < 0.01$). Age ($P < 0.01$), systolic blood pressure ($P < 0.01$), the presence of hypertension ($P < 0.01$), HbA_{1c} level ($P = 0.03$), and aspirin treatment ($P < 0.01$) were directly associated with MCA PI, and diastolic blood pressure ($P < 0.01$) and heart rate ($P = 0.06$) were inversely associated. In a multiple regression analysis, only age (β-estimate 0.0096, $P < 0.01$), systolic blood pressure (β-estimate 0.0034, $P < 0.01$), diastolic blood pressure (β-estimate 0.0055, $P < 0.01$), and the presence of retinopathy (β-estimate 0.0654, $P < 0.01$) were associated with MCA PI. When a three-level variable of DR (no, mild, and more than mild DR) was included in this model instead of a dichotomous variable (DR/non-DR), similar results were found for DR ($P < 0.01$).

Table 2—Frequency and severity of SVD (WMLs and lacunes) according to retinopathy status (No DR, mild DR, and more than mild DR)

	No DR ($n = 146$)	Mild DR ($n = 56$)	More than mild DR ($n = 87$)	*P* value
WMLs	44 (30.1)	17 (30.4)	41 (47.1)	0.02
Lacunes	4 (2.7)	4 (7.1)	6 (6.9)	0.24
SVD	44 (30.1)	18 (32.1)	42 (48.3)	0.02
High SVD score	12 (8.2)	7 (12.5)	20 (23)	<0.01

Values are reported as *n* (%) unless otherwise indicated. A patient was classified as having a higher severity of SVD score if any of the following took place: any ARWMC score and two or more lacunes, an ARWMC score of 1 and any lacunes, or an ARWMC score of 2–3 with or without lacunes.

Finally, a positive association was found between the presence or severity of SVD and the PI. Those patients with any SVD lesion (WMLs and/or lacunes) had significantly higher median values of MCA PI than those without SVD lesions ($n = 62$, 1.04 [Q1–Q3 0.93–1.25] vs. $n = 140$, 0.94 [Q1–Q3 0.85–1.09], $P < 0.01$]). Furthermore, those patients with high SVD scores ($n = 21$) had significantly higher median MCA PI values than those without SVD (see values above) or with mild SVD ($n = 181$, 1.14 [Q1–Q3 1.00–1.31] vs. 0.95 [Q1–Q3 0.86–1.10]) ($P < 0.01$ for the two comparisons).

CONCLUSIONS

The main finding of the current study is that patients with type 2 diabetes and DR, without previous CV disease, show manifestations of cerebral SVD in contrast to those patients without DR. More specifically, the presence of DR is associated with more severe SVD. Further, those patients with more severe grades of DR also show a more severe grade of SVD. Subjects with type 2 diabetes with DR also had higher MCA PI values, a measure that is indicative of distal vascular resistance. PI steadily increased according to the presence and degree of DR.

Type 2 diabetes is associated with an increased risk of stroke and cognitive decline. Regarding cerebral SVD, an increased prevalence of lacunar infarcts has been described in subjects with type 2 diabetes compared with subjects without DM (23). Further, patients with diabetes and lacunar strokes show a poorer prognosis than their nondiabetic counterparts (9). In our study, the frequency of lacunes was lower than those in previous studies, because our patients had no history of cerebrovascular disease. The association between type 2 diabetes and WMLs is less clear (24). Regarding cross-sectional studies performed in patients with type 2 diabetes who have used the same methods as ours (i.e., visual rating scales), conflicting results have been described to evaluate the presence and severity of WMLs. Some have described (6) a higher frequency and severity of WMLs compared with people without DM (7,25), especially WMLs located in the deep cerebral area, whereas others have found no differences. However, with the use of more sensitive brain magnetic resonance

techniques, recent studies (26) seem to show, more firmly than previously reported, a relationship between DM and both the presence and severity of WMLs.

In the current study, the severity of SVD was higher in patients with type 2 diabetes and DR compared with those without DR. Interestingly, a recent study by Sink et al. (8) showed that microalbuminuria was associated with an increased volume of WMLs in type 2 diabetes. Additionally, in our study, advanced grades of DR were independently associated with more severe lesions of SVD. However, we found no differences in the percentage of patients with WMLs or lacunes when both groups (patients with or without DR) were compared. The low prevalence of WMLs and lacunes found in our study could be influenced by the selection of our study population, because patients included in the current study were younger than those in previous studies and had no previous CV disease or established chronic kidney disease.

The PI, as derived from TCD, has been interpreted as a consequence of SVD due to changes in vascular resistance. In a group of 86 patients with type 2 diabetes, Lippera et al. (27) described an increased PI in those patients with proliferative DR compared with those without DR or a background of DR. These results are consistent with those reported by Lee et al. (14) that described a significantly higher PI of the MCA in a group of 33 patients with a microvascular complication who had retinopathy, nephropathy, or neuropathy.

In the current study, a positive association was found between the presence and severity of SVD and mean MCA PI values. In the general elderly population, MCA PI has been described to correlate with WML severity (28). In patients with a recent transient ischemic attack or stroke, Webb et al. (12) have recently described that MCA PI is associated with the presence and severity of leukoaraiosis and with both pulsatility and arterial stiffness in both the aorta and the MCA. Thus, the authors of this latest study suggest a causative pathophysiological relationship between WMLs and large artery stiffening. Arterial stiffness has been shown to be an independent risk factor for adverse CV events and all-cause mortality in the general population (29). In patients with type 2 diabetes, an increased pulse wave velocity in the large arteries has been described, which is a measure used for the evaluation of arterial stiffness (30). In these patients, arterial stiffness has also been reported (31) to be independently associated with the severity of cerebral WMLs. On the other hand, in patients with type 2 diabetes, DR has been independently associated with pulse wave velocity, with the severity of DR being associated with a greater peripheral vascular stiffness (32). The stiffening of large arteries such as the aorta may promote more penetration of the pulsatile energy into the microvasculature of the brain, resulting in a smaller lumen and a reduced vasodilatory reserve. Several potential mechanisms have been proposed for the arterial wall stiffening observed in patients with type 2 diabetes. To our knowledge, there are no data in the literature on the relationship among cerebral SVD, the presence and severity of retinopathy, and MCA PI values in patients with type 2 diabetes.

The current study has several limitations. A direct relationship between retinopathy and cerebral microangiopathy cannot be demonstrated because of the cross-sectional design of the study. The lack of an age-matched control group without diabetes prevents the extrapolation of these results to the general diabetic population. The frequency of the cerebral MRI findings is lower than initially expected to calculate the sample size. Therefore, although we included a large number of subjects with diabetes, the frequency of lesions of brain SVD cannot be considered as representative of the population with type 2 diabetes. Recent studies (29) have related cerebral PI to aortic and proximal large artery stiffness. We cannot rule out this hypothesis because the study was not designed for this purpose.

The strengths of the current study are its specific design, which aimed to test the hypothesis that the brain is a target organ for diabetic microangiopathy related to retinopathy. Thus, a considerable number of patients with retinopathy were included. All PI measurements were made by the same neurologist with a standardized method, and only good-quality individually revised Doppler spectrum waveform PI values were used to evaluate the measurements.

In conclusion, in the current study we found that patients with type 2 diabetes and DR have a more severe grade of SVD and a higher MCA PI compared with those without DR. These data are at the expense of those patients with more severe grades of DR. Moreover, a positive association has been found between SVD severity and MCA PI values. Future studies are needed to evaluate the usefulness of measuring the MCA PI, and the presence and severity of DR as possible markers of cerebral microvascular lesions in patients with type 2 diabetes. The results of the present study suggest that, for type 2 diabetes, DR is associated with an increased burden of cerebral SVD, supporting the hypothesis that the brain is a target organ for microvascular complications of diabetes similar to other organs such as the retina.

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